Mass transport across fluid/fluid interfaces. Release and absorption of drug from non-polar dosage forms.

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SUMMARY

Chapter 1 describes an explorative study in which the effect of various parameters on the release of drugs from fatty suppository bases is investigated. An apparatus was developed in which the release of drugs from suppositories can be measured without making use of semi-permeable membranes.
In this apparatus all the relevant phenomena determining the release process were observed. However, it was found that the release can be measured equally well from premelted suspensions in another apparatus in which a tube filled with the lipid phase is placed vertically in a water vessel producing a well defined lipid-water interface. This technique is useful if one is not interested in the melting behavior of the suppository. To investigate the release mechanism in this chapter a simple experiment is described in which drug particles are immobilized in the suppository base by using the additive Aerosil 972 by which in fact a matrix-system is prepared. By comparing a drug that is insoluble in the base (sodium salicylate) with a drug that is soluble in the lipid phase (salicylic acid) it could be shown that a mechanical transportation of the particles through the base is necessary for lipid insoluble drugs to be able to be released from the dosage form (mechanism 1) whereas diffusion is the process that may determine the release of drugs that are lipid soluble (mechanism 2). In the release apparatus the particles are sedimenting through the base, therefore it was expected that variation of particle size would have a different effect on the release for drugs that are lipid soluble and for drugs that are quite insoluble in lipid. Indeed it was found that particle size variation greatly affected the release of lipid insoluble drugs, whereas this parameter only slightly influenced the release of the lipid soluble drugs. However, it will be shown in chapter 3 that sedimentation normally is not the rate determining step. It was concluded from these results that the influence of particle size seemed to be connected with the release mechanism (See: chapter 2).

The higher release rate that was measured for a micronized fraction of a lipid soluble drug as compared with the release rate of the same fraction of a drug that is insoluble in lipid is explained in chapter 3.

In chapter 2 it is reported that within the group of drugs that are insoluble in lipid, two categories of drugs should be distinguished: 1, drugs that dissolve rapidly in water such as sodium salicylate, and 2, drugs that dissolve slowly in water, for instance paracetamol.
The release flow of various size fractions of paracetamol from a lipid phase was measured. It appeared that below a certain concentration of paracetamol (< 1%) particle size variation influences the release flow in the same manner as was measured for drugs that are highly soluble in water. However in a higher concentration range, particle size and also concentration of the drug particles had no effect on the release flow at all. In fact, in that case paracetamol showed a release pattern that was similar to the release behavior of lipid soluble drugs.
In this chapter the release behavior of drugs that are insoluble in lipid is described according to a two compartment system.
The first compartment is the lipid phase in which particle transport is taking place, the second compartment is the aqueous phase in which the drug particles dissolve. For drugs that are rapidly dissolving in water, the overall release rate is determined by the rate of the particle transport in the lipid phase. For drugs that dissolve slowly in water, particle transport in the base is fast enough to cover the interface completely with particles. Here the dissolution rate of the drug particles at the interface determines the overall release rate.
If lipid soluble drugs are present in the lipid phase as a suspension, particles are dissolving only at the interface, since the saturation concentration is reached in the bulk of the lipid phase. Therefore it is concluded that for such drugs the same model is applicable as for drugs that are slowly dissolving and that are insoluble in lipid.

The lipid solubility is associated with a low water solubility and therefore for these drugs also a rate limiting step occurs in the second compartment.
If lipid soluble drugs are present in a concentration that is lower than the saturation concentration, diffusion of the drug in the lipid phase is the rate limiting process, because the viscosity of the base is considerably higher than the viscosity of the aqueous phase.
Based on the data measured *in vitro* for slowly dissolving drugs it was postulated that *in vivo* the rate of absorption should be independent of the concentration of these drugs in the suppository. Also it was postulated that an influence of particle size on absorption rate will only be caused by a different spreading of the particles along with the base, so that *in vivo* the area of interface that is covered with particles would be different. Since the volume of the suppository determines the area of interface, this parameter should have an effect on absorption rate for slowly dissolving drugs in the rectal lumen in man.
Moolenaar (thesis 1979) was able to verify these hypotheses for paracetamol *in vivo*, whereas the behavior of lipid soluble drugs (for instance: acetylsalicylic acid) could also be explained.

In chapter 3 a study is reported concerning the particle transport in a lipid phase for the highly water soluble drug sodium salicylate. It is shown by sedimentation and release measurements that small particles are sedimenting rapidly in the lipid phase due to agglomeration. However, above a certain concentration the release flow reached a maximum whereas sedimentation flow was still increasing. This phenomenon was also described for paracetamol, but in the case of sodium salicylate this maximum release flow depended strongly on particle size.
Therefore a rate limiting step in the dissolution process was considered to be unlikely. Based on the release measurements, a rate limiting step in the particle transport through the bulk of the lipid phase was also excluded.

Therefore a resistance present at the lipid side of the interface that is dependent on particle size was proposed. The wetting process in itself is very fast for crystals of sodium salicylate (a fraction of a second), but in the literature (Reynolds 1886; Hartland 1968) the "viscous drainage process" is described that might be responsible for the observed resistance. It is shown by these authors that after sedimentation of a plate or a sphere into the direction of a fluid/fluid interface it takes some time before the drainage of the film of the upper fluid between the solid body and the interface has been completed and the solid body is wetted.
In this chapter an equation is derived expressing that drainage and dissolution of particles at an interface together determine the release rate of the drug. The experimental values found for the maximum release flow of various size fractions of sodium salicylate were fitted with this equation. The parameters obtained with this curve fit allowed the following conclusions: 1. Drainage time itself is independent of particle size. 2. The particle size effect, that is measured for sodium salicylate, is caused by the fact that a reduction in size of the particles for a certain weight of drug is proportional to the number of times the interface has to be crossed for that same weight of drug. Therefore, if the drainage time is in the same order of magnitude as dissolution time, this process may to a large extent determine the release rate. It was demonstrated that the drainage process is important for the release of highly soluble drugs from suppository bases. The difference in release rate between small particle sizes of drugs that are soluble in the lipid phase and that are insoluble in the lipid phase (chapter 1) is shown to be caused by the drainage process.
It could be shown that very probably the drainage process also is operating in vivo. Furthermore it was shown that addition of talcum, a material that does not dissolve in water or in lipid results in a very low release and absoption rate. This is probably due to the fact that the particles of talcum are covering the interface, creating an effective resistance for the drug particles.

Chapter 4 describes a study that was performed to evaluate the influence of the composition of a number of suppository bases, available in the Netherlands, on release rate. A drug was chosen that dissolves rapidly in the aqueous phase (sodium benzoate), in order to detect differences in particle transport, caused by the composition of the bases. A micronized fraction and a coarse fraction (125-250 μm) of this drug were investigated in vitro and in vivo. For the micronized fraction only small differences could be detected for the release in vitro and the absorption in vivo of sodium benzoate from the four bases.

In contrast the coarse fraction showed a significant retardation in absorption of the drug from cocoabutter and Massuppol in vivo in comparison with Witepsol H 15. It was shown in vitro that at the interface of cocoabutter or Massuppol and water an elastic emulsion layer developes, the formation of which is promoted if particles are crossing the interface. Since the micronised fraction did not show a hampered transport across the interfaces of cocoabutter and Massuppol, it is obvious that it is a property of the coarser particles that makes these particles sensitive for the interfacial resistance.

An inspection of the coarse fraction of sodium benzoate particles revealed that these particles are soft aggregates of finely pulverized material, whereas for instance sodium salicylate particles are crystals.

An investigation in vitro showed that the release of sodium salicylate from cocoabutter was not slower compared with the release from Witepsol H 15. In vivo, as judged by the absorption rate data, this appeared also to be true (Moolenaar 1979), therefore it was concluded that sodium benzoate is released at a slower rate from cocoabutter and Massuppol by a combined effect of the aggregated state of its coarse particles and the elastic emulsion layer formed by the two bases mentioned.

Benzoic acid was used to measure differences in spreading of the bases due to their composition.

Although in vitro significant differences were measured between cocoabutter and Massuppol on one side and Estarinum and Witepsol H 15 on the other side, in vivo measurements showed no significant differences. Probably the abdominal pressure on the rectum wall is the predominant factor in the spreading behavior of suppository bases.

In chapter 5 a study is presented in which the influence of particle size on dissolution rate of single crystals is investigated An apparatus was developed in which crystals of potassium ferricyanide could be observed at a liquid paraffin-water interface. Since the equilibrium position of a crystal at the interface was found to be independent of its size, the lifetime of a crystal dissolving at the interface is determined entirely by its initial size and its dissolution rate in the aqueous phase. The dimensions of the individual crystals were measured microscopically before dissolution. In this way the total area of the crystal faces available for dissolution could be calculated beforehand.
Experimentally the rate of retreat of the dissolving surfaces was measured separately for the vertical and the horizontal faces of the crystal; in this manner it was possible to quantitatively describe the flow of dissolved mass as a function of particle size.
The area under the theoretically calculated curves appeared to be similar to the area under the curves measured experimentally, indicating that the measurement of dimensions and dissolution rates was reasonable accurate.
In chapter 5 three equations are derived for the dissolution of potassium ferricyanide crystals at the interface, in which:
For equation 1 an idealized shape is assumed for the crystals and only one dissolution rate constant for all crystal faces is considered ("cube root law" dissolution).
For equation 2 an idealized shape is assumed and two rate "constants" are considered: one for the vertical faces and one for the horizontal face and for equation 3 the precize shape is used and two rate "constants" are considered as mentioned under 2.

It was concluded: 1) that all vertical faces of the crystals are dissolving with a constant rate and the shortest dimension of the face that is in contact with the liquid paraffin determines the lifetime of a crystal; 2) that the horizontal face is dissolving non-linearly and at a rate that is lower than the rate measured for the vertical faces. It is concluded that the non-isometric dissolution behavior of the crystals greatly affects the shape of the curve.

In chapter 6 an investigation is described concerning the influence of particle concentration at an interface on the dissolution rate. In such a multiparticulate system it appeared that the vertical faces of the particles are dissolving considerably slower as compared with single particle dissolution due to a rate limiting step in the transport of dissolution medium to the crystal faces. In contrast the vertical faces at the circumference of the multiparticulate system and the horizontal faces of all particles are dissolving at the same rates as was measured for single particles. Therefore, one may visualize a dissolving multiparticulate system as a very large crystal. It is of interest to note that a tablet surface has about the same mass flux as a multiparticulate system, whereas for the latter a porosity is measured of 40 percent. Theoretically four models are developed and compared with each other by means of a model factor (k_m) in which a different value for each model is proposed (for model 3 a series of values is possible). Since k_m can be determined experimentally it is possible to choose the model that describes dissolution of a multiparticulate system best. It is concluded that the third and the fourth model, or a combination of the two, are most probable. Both models include an assumption considering the growth of pores in between the dissolving crystals. The similarity between dissolution of a multiparticulate system and tablet dissolution is evident for model 3, because in this model the mass flux from a pore is considered to be constant.

Since the third model is requiring a geometrical distribution of pores at the interface, it will be attempted to demonstrate such a distribution experimentally in the future.

REFERENCES

Moolenaar, F., (1979), Biopharmaceutics of rectal administration of drugs in man, Ph. D. Thesis. University of Groningen, The Netherlands.